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10/777,683	02/13/2004	Richard B. Moss	Q74236	5880

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EXAMINER	
FOSTER, CHRISTINE E	

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1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/777,683	MOSS ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/28/08*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicant's amendment, filed 7/28/08, is acknowledged and has been entered. Claim 1 was amended. Claims 4-8, 11-15, 17-18, and 21-23 were canceled. New claim 24 was added. Accordingly, claims 1 and 24 are currently pending and subject to examination below in light of the elected species of **diagnosis**.

Objections/ Rejections Withdrawn

2. The rejections of claims 4-8, 11-15, and 21 are moot in light of Applicant's cancellation of these claims.

3. The rejection of claim 1 under § 112, 1st paragraph as set forth in the previous Office action (new matter) has been obviated by Applicant's amendments to the claim.

4. The rejections under § 102 have been withdrawn in response to Applicant's amendments to include the limitations of claims 8 and 15 (now canceled) into the independent claim.

Priority

5. The present application was filed on 2/13/2004 and claims benefit under 119(e) to provisional application No. 60/447,310, filed on 2/14/2003.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Independent claim 1 recites a method of measuring the level of "native CAP 18". However, the use of the designation "**CAP 18**" alone to describe a particular protein renders the claims indefinite because different laboratories may use the same laboratory designation to define completely distinct proteins or protein fragments. The evidence of record indicates that indeed, this is true in the instant case: the specification discloses that "the entire amino acid sequence of human CAP 18 is…SEQ ID NO:4" (see p. 7), which is a 170-amino acid protein. However, Montelaro et al. (US 6,835,713 B2) describe human CAP 18 (hCAP18) as being a 37-amino acid peptide (see column 1, lines 57-61). By contrast, Applicant's postfiling work (Xiao et al., discussed above) identifies human CAP18 as a 140-amino acid protein (see p. 2317, left column, the first paragraph). As such, it is not clear what species is being detected since the claim refers only to "native CAP 18" but does not adequately identify the sequence of the protein to be detected.

While the specification discusses how the entire sequence of human CAP 18 is SEQ ID NO:4, the term "CAP 18" encompasses a genus of proteins and is clearly not limited to SEQ ID NO:4. (see the specification at page 7, last full paragraph).

Although the claim also refers to "native" CAP 18, this descriptor fails to clarify the scope of the claim since the specification indicates that the term "native" refers simply to "non-mutated" CAP 18 (page 7, last full paragraph). Therefore, while "native CAP 18" would indicate a non-mutated protein, it is still unclear whether Applicant intends detection of a non-mutated

37-amino acid peptide, a non-mutated 140-amino acid protein, a non-mutated 170-amino acid protein, etc. For all of these reasons, the metes and bounds of the claim are unclear.

9. Claim 24 is also indefinite in reciting "CAP 18" for the reasons discussed above. Amendment of the claims to recite the SEQ ID NO may obviate the above rejections.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bals et al. ("Salt-Independent Abnormality of Antimicrobial Activity in Cystic Fibrosis Airway Surface Fluid" *Am. J. Respir. Cell Mol. Biol.* **25** (2001), pages 21-25) in view of Weinberg et al. (US 6,187,536 B1) and in light of the evidence of iHOP (Information Hyperlinked over Proteins –

data for CAMP, cathelicidin antimicrobial peptide, p. 1, downloaded from http://www.ihop-net.org/UniPub/iHOP/gs/86912.html on 01/04/2007).

Bals et al. teach measuring the level of CAP 18 ("LL-37/hCAP-18") in biological samples from humans (bronchoalveolar lavage fluid and human bronchial xenografts generated from respiratory epithelial cells of children) and comparing the levels in cystic fibrosis patients with those of normal control patients (see the entire document, in particular the abstract; p. 21, right column; p. 22, left column; Figures 3-4; and p. 23-24, "Concentrations of Known Antimicrobial Peptides Are Equivalent in CF and Normal ASF").

The protein detected by Bals et al. (LL-37/hCAP-18) is "CAP 18" in light of the evidence of iHOP, which teaches that hCAP-18, CAP-18, and LL37 are synonyms that designate the same protein (page 1, top right). The protein measured by Bals et al. would also be considered to be "native" (i.e., non-mutated as this term is employed by Applicant in the instant specification) since the reference refers to the CAP 18 protein present *in vivo* in biological samples such as human BALF, which is also disclosed as a sample source in the instant specification.

In addition, Bals et al. detected CAP 18 using an antibody raised against the same portion of SEQ ID NO:4 as Applicant's disclosed antibodies: the disclosed antibodies were raised against SEQ ID NOs1-3, which all fall within the same 37-amino acid region that was also used to raise the antisera of Bals et al.). See Bals et al. at page 21, "Preparation of Antibodies…". Since Bals et al. employed antibodies having the same specificity to detect protein in the same sample source as Applicants, there is a strong scientific basis to believe that the methods of Bals et al. also necessarily detects the same protein, i.e. "native CAP 18", even though the reference does not employ this exact terminology. For all of these reasons, and absent evidence that the prior art

method would not necessarily detect "native CAP 18", the reference reads on the claim limitation. See MPEP 2112 (IV).

With respect to the step of "diagnosing a possibility of cystic lung fibrosis", Bals et al. clearly identify that cystic fibrosis patients were included in the study, such that their diagnosis with cystic fibrosis would be at once envisaged by one of ordinary skill in the art. Such a teaching reads on the claims because there is no recited connection between diagnosis and measurement of CAP 18 levels; the claims separately recite measurement of CAP 18 and do not clearly require that diagnosis is performed *based on the results of the measurement*. Therefore, when the claims are given their broadest reasonable interpretation, diagnosis is not necessarily made based on differences in CAP 18 levels between test and control samples.

Furthermore, the claim terminology "diagnosing a possibility of" disease may be interpreted broadly and could refer simply to the recognition of the signs and symptoms of disease, or to analysis of the nature or cause of disease[1]. Bals et al. identified a subset of patients as having cystic fibrosis and also performed studies to document the signs and symptoms of this disease. For example, Bals et al. also documented abnormalities in antimicrobial activity in cystic fibrosis (page 22, "Results"). In addition, the genetic defects underlying the fibrosis patients' disease were determined by Bals et al. (see the paragraph bridging pages 21-22). Such teachings in which Bals et al. recognized the signs and symptoms of cystic fibrosis and also

[1] See the Merriam-Webster Online Dictionary, which includes the following definitions for the term "diagnosing": **1 a :** to recognize (as a disease) by signs and symptoms **2 :** to analyze the cause or nature of <*diagnose* the problem> (retrieved from http://www.merriam-webster.com/dictionary/diagnosing on 10/9/08).

analyzed the genetic cause or nature of disease, would read on the claimed step of diagnosing a possibility of cystic fibrosis.

For all of these reasons, when the claims are given their broadest reasonable interpretation the teachings of Bals et al. read on the claimed step of diagnosis even though the reference does not specifically mention assigning patients with a possible diagnosis of cystic lung fibrosis based on increased CAP 18 levels.

Bals et al. measured CAP18 by dot-blot and immunoblot assay using polyclonal antisera (se p. 21, right column, "Preparation of Antibodies..." and p. 22, left column, "Determination of Peptide Concentrations..." and Figure 4). In particular, an antibody was raised against LL-37/hCAP-18 containing the C-terminal 37 amino acids (see p. 21, right column, "Preparation of Antibodies..."). As can be seen in the instant sequence listing for the entire amino acid sequence of CAP 18 provided by Applicant as SEQ ID NO:4, SEQ ID NO: 1 is included within the last 37 residues of the protein (see the sequence listing filed 9/20/04). Therefore, the 37-residue peptide taught by Bals et al. is "a peptide having an amino acid sequence of SEQ ID NO:1", and the antibodies raised thereto would bind to the peptide.

The teachings of Bals et al. therefore differ from the claimed invention in regards to the method used to detect CAP18: Bals et al. exemplify measuring CAP18 by dot-blot and immunoblot assay, but fail to specifically teach measuring CAP 18 using a sandwich-type, two-antibody immunoassay format as recited instantly.

However, such sandwich immunoassay formats and their advantages were well known in the art at the time of the invention. For example, Weinberg et al. teach immunoassays comprising the steps of bringing into contact a solid phase support in which a first anti-protein antibody is

immobilized with a test sample to form a complex or "sandwich" (see column 21, line 44 to column 22, line 7). Subsequently, the complex is detected either via a detectable second antibody or a third detectable antibody. Weinberg et al. teach that in contrast with simple immunoassays such as dot blot or Western blot, "two-site" or "sandwich" assays as detailed above provide excellent results and can be made quantitative.

Therefore, it would have been obvious to one of ordinary skill in the art to employ the sandwich immunoassay format taught by Weinberg et al. in order to measure CAP 18 in the method of Bals et al. In particular, it would have been obvious to contact the samples of Bals et al. with a first antibody specific to CAP 18 (which is a peptide "having" an amino acid sequence of SEQ ID NO:1 as recited in step (a)' of claim 1) immobilized on a solid phase and to quantify the amount of CAP 18 using a second, directly or indirectly labeled antibody specific to CAP 18. One would be motivated to combine the reference teachings in this manner because Weinberg et al. taught that such immunoassays provide excellent results as compared with simple dot blot or Western blot assays, which are the methods used in Bals et al. Therefore, one would have been motivated to substitute the two-antibody sandwich immunoassay format of Weinberg et al. for the dot-blot or immunoblot formats exemplifed by Bals et al. because the former were recognized by the prior art to provide superior results than the latter.

Regarding claim 24, Weinberg et al. teach both polyclonal and monoclonal antibodies (column 22, lines 8-10). When taken together with the general knowledge in the art, one of ordinary skill in the art would have found it obvious to employ either polyclonal and/or monoclonal CAP-18-specific antibodies when conducting the sandwich immunoassay for CAP-

18 and would have recognized that the results of combining these known prior art elements would have achieved predictable results.

Response to Arguments

13. Applicant's arguments in the Reply of 7/28/08 have been fully considered.

14. With respect to the rejection of claim 1 under § 112, 2nd paragraph as being indefinite in reciting "CAP 18", Applicant argues that the instant amendments to recite "native cationic antimicrobial protein of 18 kDa", have obviated the grounds of rejection (Reply, pages 5-6).

This is not found persuasive because although it is acknowledged that the term "CAP 18" is an abbreviation for "cationic antimicrobial protein of 18 kDa", which includes therein a reference to the molecular weight of the protein, in this case the evidence of record indicates that those of skill in the art did not employ the term "CAP 18" to refer exclusively to the 18-kDa, 170-residue form of the protein. Rather, while Applicant argues that "CAP 18" would refer only to the 170-residue form, Applicant has used this same terminology to refer to a 140-residue protein, as discussed in the rejection.

Applicant argues that the term "native CAP 18" is well known to one of ordinary skill in the art to refer to a 170-residue protein (Reply, pages 5-8). Applicant also points to the description of CAP 18 in the instant specification (Reply, pages 6-7). However, no specific or limiting definition could be found therein that would clarify what protein(s) is meant by "native CAP 18". Rather, it is disclosed that "the expression "CAP 18,"...encompasses proteins having slight structural differences from native (non-mutated) CAP 18". Therefore, the definition in the

specification is not limited to a 170-residue protein but rather would encompass a genus of proteins.

Applicant further points to a non-patent literature publication by Larrick et al. (Reference 1) which discusses the presence of a 30-amino acid signal sequence found on human CAP 18 (Reply, page 7). The Examiner does not see how such remarks would serve to clarify the scope of the term "CAP 18" as used instantly. Larrick et al. do not specifically define "CAP 18" as referring only to the entire protein including the signal sequence.

Even if the teachings of Larrick et al. could be construed in this manner, the evidence of record still indicates that others used the same term "CAP 18" to refer to different proteins, as discussed in the rejection.

In addition, Applicant is reminded that "Essential material", i.e. material necessary to describe the claimed invention in terms that particularly point out and distinctly claim the invention as required by the second paragraph of 35 U.S.C. 112, may be incorporated by reference, but only by way of an incorporation by reference to a U.S. patent or U.S. patent application publication.

Applicant also points to U.S. Patent No. 5,615,675 (Reference 2) but the citation indicated appears to be incorrect, as the inventor of this patent is not Larrick et al. as indicated by Applicant. No discussion of CAP 18 could be found in U.S. Patent No. 5,615,675.

Applicant also points to two websites (References 3 and 4); as above, incorporation of essential material may only be made by reference to a U.S. patent or U.S. patent application publication. Furthermore, Applicant has not submitted a copy of the material desired for consideration and the contents of websites are subject to change over time.

Therefore, it is maintained for reasons of record that the descriptor "native CAP 18" is insufficient to identify the intended protein or protein fragment being detected by the method, which renders the scope of the claims indefinite.

15. With respect to the rejections under § 103 as being unpatentable over Bals et al. in view of Weinberg et al., Applicant's arguments (Reply, pages 9-12) have been fully considered but are not persuasive.

Applicant argues that the claims have been amended to positively recite diagnosis of possible cystic fibrosis based on CAP 18 levels (Reply, page 10), to which the Examiner disagrees. Applicant also argues that Bals et al. do not teach a significant difference in CAP 18 levels between disease patients and controls (Reply, pages 10-11).

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., that the claims require diagnosis based on differences in CAP 18 levels) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). There are no steps clearly recited in the claims that convey that diagnosis is made based on CAP 18 levels. Consequently, whether Bals et al. teaches a significant difference in CAP 18 levels between cystic fibrosis patients and controls is tangential to the patentability of the currently presented claims, which do not require that a diagnosed be conferred based on differences in CAP 18 levels as compared to control levels.

Applicant further argues that the method described enables diagnosis of CF patients, and that such an effect cannot be easily expected (Reply, page 11). As best understood, Applicant argues for unexpected results.

This is not found persuasive because whether evidence shows unexpected results is a question of fact and the party asserting unexpected results has the burden of proving that the results are unexpected. In re Geisler, 116 F.3d 1465, 1469-70, 43 USPQ2d 1362, 1364-5 (Fed. Cir. 1997). The evidence must be (1) commensurate in scope with the claimed subject matter, In re Clemens, 622 F.2d 1019, 1035, 206 USPQ 289, 296 (CCPA 1980), (2) show what was expected, to "properly evaluate whether a ... property was unexpected", and (3) compare to the closest prior art. Pfizer v. Apotex, 480 F.3d 1348, 1370-71, 82 USPQ2d 1321, 1338 (Fed. Cir. 2007). In the instant case, Applicant has neither clearly explained nor documented what features were unexpected. Further, the claims are not limited to diagnosis of cystic fibrosis patients with "significant difference", such that the allegations regarding unexpected results are not commensurate with the claim scope. For all of these reasons, the arguments by counsel are not considered to be sufficient evidence of unexpected results.

Conclusion

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 6:30-3:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya, can be reached at (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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